IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPELLANTS:	Weihong Xiong et al.
SERIAL NO:	10/723,435
FILED:	11/26/2003
FOR:	TRANSDERMAL ADMINISTRATION OF HUPERZINE
ART UNIT:	1611
EXAMINER:	Isis A D Ghali
DOCKET NO.:	01121-T8341.NP.CON

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

DATE OF DEPOSIT: **February 12, 2009**

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/Nicole Solomon/
Nicole Solomon

APPELLANTS' APPEAL BRIEF UNDER 37 C.F.R. § 41.37

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Mail Stop Appeal Brief – Patents

Dear Sir:

Appellants submit this appeal brief in connection with their appeal from the final rejection of the Patent Office, mailed September 22, 2008, in the above-identified application. A Notice of Appeal was filed on December 8, 2008.

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I. REAL PARTY IN INTEREST

The real party in interest is Xel Herbaceuticals, Inc., a corporation under the laws of the State of Delaware and having a principal place of business at 12382 Gateway Park Place, Ste B800 Draper, UT 84020.

II. RELATED APPEALS AND INTERFERENCES

Appellants and Appellants' legal representatives know of no other appeals or interferences that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 81-84, 86, 102, and 103 remain pending and have been rejected. Claims 1-52, 85, and 98-101 have been canceled and claims 53-80 and 87-97 have been withdrawn. The claims on appeal in this application are claims 81-84, 86, 102, and 103.

IV. STATUS OF AMENDMENTS

Appellants submit for the record that no amendments have been made in the present application after the Final Office Action. All amendments made in prosecution prior to that Action have been entered.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The subject matter of the claims at issue in this appeal may be summarized as follows (with references in brackets indicating the location in the specification where said subject matter may be found):

Claim 81 provides a method of improving memory and cognitive function in a subject [page 10, lines 15-17, comprising:

transdermally administering huperzine to the subject from a transdermal matrix patch [page 32, line 23 to page 33, line 4; Page 33, lines 6-9] that includes an adhesive matrix with an acrylate polymer including homopolymers, copolymers, or terpolymers, or rubber-based pressure sensitive adhesive including copolymers [Page 33, lines 15-19; Page 35, line 23 to Page 35, line 9] and a fatty acid ester of lactic acid as a permeation enhancer [Page 23, lines 13-19], said matrix patch excluding Azone [page 23, lines 15-19, 20-23; page 24 lines 1-6], in order to provide a huperzine blood plasma level of from about 0.1 to about 30 ng/ml for a duration of at least about 3 days from a single transdermal administration [page 7, line 20 to page 8, line 1; page 11, lines 2-5].

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issue presented for review is whether claims 81-84, 86, 102, and 103 are unpatentable under 35 U.S.C. 103(a) as being unpatentable under 35 U.S.C. 103(a) as being obvious over U.S. Patent No. 6,352,715 (hereinafter U.S. '715) in view of U.S. Patent No. 6,365,178 (hereinafter U.S. '178)

VII. ARGUMENT

A. Appellants' Invention

Appellants' invention is outlined in independent claim 81, which states:

A method of improving memory and cognitive function in a subject, comprising:

transdermally administering Huperzine to the subject from a transdermal matrix patch that includes an adhesive matrix with an acrylate polymer including homopolymers, copolymers, or terpolymers, or rubber-based pressure sensitive adhesive including copolymers and a fatty acid ester of lactic acid as a permeation enhancer, said matrix patch excluding Azone, in order to provide a Huperzine blood plasma level of from about 0.1 to about 30 ng/ml for a duration of at least about 3 days from a single transdermal administration.

B. The Asserted References

1. U.S. '715 Reference

U.S. '715 is drawn to a transdermal delivery system for Huperzine A. Abstract. Generally, the '715 reference focuses on pH as a means to increase permeation of the drug and concludes that the only form of Huperzine able to penetrate the skin is the neutral form. Col. 2, lines 65-67. The '715 reference speculates that a possible method to further improve delivery of the neutral form of Huperzine is to increase concentration of undisassociated Huperzine at the Huperzine source by adding non-polar solvents such as alcohols and glycols. Col. 8, lines 41-49.

2. U.S. '178 Reference

U.S. '178 is drawn to a method of making pressure sensitive matrix patches for transdermal delivery of drugs. Abstract. The method includes the steps of dissolving a

hydrophilic salt form of the drug in the water phase of an aqueous dispersion of a hydrophobic pressure sensitive adhesive, casting the mixture, and evaporating the water. Abstract. U.S. '178 teaches a lengthy list of drug classes and numerous envelope disordering compounds which can be incorporated into the pressure sensitive matrix.

C. Rejection Under 35 U.S.C. § 103(a)

1. Requirements for *Prima Facie* obviousness

The Examiner has rejected claims 81-84, 86, 102, and 103 under § 103(a) as allegedly being *prima facie* obvious over U.S. '715 in view of U.S. '178. The Patent and Trademark Office (PTO), through the Examiner, has the burden of establishing a *prima facie* case of obviousness. *In re Fine*, 837 F.2d 1071, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1998). To satisfy this burden, the PTO must set forth a *prima facie* case of obviousness under any one of the rationales identified by the Supreme Court in *KSR International Co, v. Teleflex, Inc.* (550 U.S. 398) (2007). Such rationales can be found in MPEP § 2143, and include:

1) Combining prior art elements according to known methods to yield predictable results;

2) Simple substitution of one known element for another to obtain predictable results;

3) Use of known technique to improve similar devices (methods, or products) in the same way;

4) Applying known technique to a known device (method, or product) ready for improvement to yield predictable results;

5) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

6) Known work in one field of endeavor may prompt variations of it for use in either the

same field or a different one based on design incentives or other market forces if variations are predictable to one of ordinary skill in the art;

7) Some teaching, suggestion, or motivation in the prior art [including the references themselves and/or the knowledge generally available to one of ordinary skill in the art] that would have led one of ordinary skill in the art to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. (TSM Test)

In addition to the rationales set forth above, the obviousness analysis must comply with the statutory scheme as explained by the Supreme Court in *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966), namely, consideration must be given to: (1) the scope and content of the prior art, (2) the differences between the prior art and the claimed invention, (3) the level of ordinary skill in the pertinent art, and (4) additional evidence, which may serve as indicia of non-obviousness.

An excellent summary of how the prior art must be considered to make a case of *prima facie* obviousness is contained in *In re Ehrreich et al.*, 220 U.S.P.Q. 504, 509-511 (CCPA 1979). There the court states that a reference must not be considered in a vacuum, but against the background of the other references of record. It is stated that the question of a § 103 case is what the reference(s) would "collectively suggest" to one of ordinary skill in the art. However, the court specifically cautioned that the Examiner must consider the entirety of the disclosure made by the reference and avoid combining them indiscriminately.

In finding that the "subject matter as a whole" would not have been obvious in *Ehrreich* the court concluded:

> "Thus, we are directed to no combination of prior art references which would have rendered the claimed subject matter as a whole obvious to one of ordinary skill in the art at the time the invention was made. The PTO has not shown the existence of all the claimed limitations in the prior art or any suggestion leading

to their combination in the manner claimed by applicants." (underlining added)

It has been widely recognized that virtually every invention is a combination of elements and that most, if not all, of these will be found somewhere in an examination of the prior art. This reasoning lead the court, in *Connell v. Sears, Roebuck & Co.*, 220 U.S.P.Q. 193, 199 (Fed. Cir. 1983) to state:

> "...it is common to find elements or features somewhere in the prior art. Moreover, most if not all elements perform their ordained and expected function. The test is whether the claimed invention as a whole, in light of all the teachings of the references in their entireties, would have been obvious to one of ordinary skill in the art at the time the invention was made." (underlining added)

With the above background in mind, Appellants contend that the Examiner has not met this burden with respect to any of the claims on appeal. Particularly, Appellants submit that the PTO has failed to show that each and every element of the claimed invention is contained in the combined references. Appellants now turn to a discussion of the rejection at issue, and the references on which they are based.

2. The Rejection over U.S. '715 in view of U.S. '178

Claims 81-84, 86, 102, and 103 stand finally rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. '715 in view of U.S. '178. The Examiner cites U.S. '715 as teaching a transdermal drug delivery system to administer Huperzine A in a controlled release skin patch designed for once-a-week administration to treat Alzheimer disease. However, the Examiner concedes that U.S. '715 fails to teach the claimed blood plasma levels of Huperzine. The Examiner further concedes that U.S. '715 does not teach the transdermal device having an adhesive matrix and the claimed permeation enhancers. The Examiner attempts to cure the

deficiencies by citing to U.S. '178.

U.S. '178 is drawn to a method of making pressure sensitive adhesive matrix patches for transdermal drug delivery. The disclosure is not drawn or focused on any particular drug, but rather U.S. '178 discloses numerous broad categories or classes of drugs which could be included in matrix patch using the method of the invention. Some of the broad classes include anti-inflammatory agents, antipsychotics, anticonvulsants, antiparkinsonism drugs, vasodilators, etc. The complete listing includes in excess of 40 different categories or classes of drugs. U.S. '178 further provides a similarly broad and lengthy list of cell envelope disordering compounds or permeation enhancers. U.S. '178 provides extremely limited teachings or correlation of specific active agents with specific permeation enhancers and provides no teaching correlating fatty acid esters of lauryl alcohol with antiparkinsonism drugs, let alone huperzine.

Although the Examiner has not expressly stated which obviousness rational she relies on, it appears that the Examiner has applied the TSM test, set forth above as rational No. 7. In forming the above described combination, the Examiner has not relied on any teaching, suggestion, or motivation found in the cited references themselves to form the cited combination nor has the Examiner provided any finding that there was reasonable expectation of success. Rather the Examiner has relied on a broad and unsubstantiated assertion that the necessary teaching, suggestion, or motivation to combine the references teachings was in the knowledge generally available to one of ordinary skill in the art. Appellants vigorously dispute the Examiner's assertion of the knowledge of the ordinary skill in the art.

Transdermal drug delivery is a very complex and delicate art. For example, the identification of specific permeation or penetration enhancers for specific active agents is an extremely difficult and complicated challenge. The Appellants submit that such teachings

regarding the fickle and unpredictable nature of penetration enhancers are generally known in the art. There are numerous examples of third party teachings regarding the difficulty of formulating transdermal matrix patches, and in particular selecting and formulating with permeation enhancers. For example, U.S. Patent No. 5,500,222 states the following regarding permeation enhancers:

> No "universal" permeation enhancer has been identified. Instead, the behavior of permeation enhancers is highly idiosyncratic; a permeation enhancer effective for one drug may not be effective with other drugs, including closely related drugs.
>
> Often, a permeation enhancer will exacerbate irritation and sensitization problems by allowing high transdermal permeation rates of the drug or permeation enhancer or permitting otherwise impermeable components of the transdermal device to enter the skin. Many potential permeation enhancers interact adversely with other components of transdermal devices. One major problem is that many potential permeation enhancers are not compatible with medically acceptable contact adhesives. Enhancers may improve the transdermal permeation rate adequately, but not adequately reduce the lag time.
>
> The use of a permeation enhancer in any transdermal drug delivery device necessarily complicates the design and development of the device. Permeation enhancers cause compatibility problems throughout the delivery system. Instead of having to characterize the properties of the reservoir compositions, adhesives, and release-controlling materials with respect to just the drug, these materials must now have the proper characteristics with respect to both the drug and the permeation enhancer. Typically, drugs and permeation enhancers have very different physical and chemical properties, and, in most cases, the properties of mixtures of the drug with the permeation enhancer are unknown. For example, permeation enhancers can cause, among other problems, cohesive failure of adhesives and can partition through other components in the system.

Col. 2, line 47 through col. 3, line 12 (emphasis added).

Another third party statement which supports Appellants assertion regarding the unpredictability of formulating with permeation enhancers in the transdermal arts is found in U.S. Patent No. 7,214,381 which states in part:

> To be accepted a permeation enhancer or combination thereof should have the ability to enhance the permeability of the skin for the drug, should be non-toxic, non-irritant and non-sensitizing on repeated exposure. It is often difficult to predict which compounds will work as permeation enhancers and which permeation enhancers will work for particular drugs. In transdermal drug delivery applications, a compound that enhances the permeability of one drug or a family of drugs may not necessarily enhance the permeability of another drug or family of drugs.... Therefore, the usefulness of a particular compound(s) or mixture thereof as a permeation enhancer must be carefully analyzed and demonstrated by empirical work.

Col. 2, lines 4-20 (emphasis added).

A still further example of a third party teaching regarding the complexity of formulating transdermal compositions with permeation enhancers, particularly with regard to their interaction with other components of the transdermal formulation, can be found in U.S. Patent No 6,267,984 which states:

> In addition to these permeation enhancer-skin interaction considerations, a permeation enhancer must also be evaluated with respect to possible interactions with the transdermal system itself. For example, the permeation enhancer must be compatible with the drug to be delivered, the adhesive, and the polymer matrix in which the drug is dispersed. The permeation enhancer should also be selected to ensure suitable balance among tack, adhesion, and cohesive strength of the adhesive.

Col. 2, lines 1-9.

Appellants submit that the above teachings regarding the difficulty of formulating transdermal systems and identifying permeation enhancers are ample evidence the knowledge of those of ordinary skill in the art. Specifically, Appellants assert that the above passages demonstrate that, based on the knowledge in the art, of one of ordinary skill in the art would not have had reason to combine the cited references nor would they have had reasonable expectations of success in forming such a combination in a manner as required by the present claims. In fact, the very reference cited by the Examiner, U.S. '715, provides additional evidence regarding the difficulty and unpredictability of formulating with permeation enhancers when it states: "[a] possible method to increase the concentration of undisassociated form of Hup A may be to add non-polar solvents such as alcohols and glycols. However, these agents also reduce partitioning of drugs into the skin. Thus various co-solvents need to be evaluated to achieve balance of satisfactory solubility and partitioning." Col. 8, lines 47-52 (emphasis added).

In light of the above discussion, Appellants assert that the Examiner has not established a *prima facie* case of obviousness. Specifically, the Examiner has not shown proper teaching, suggestion, or motivation found in either the references themselves to support the presently asserted combination. Further, as set forth above, the Examiner's assertion that one of ordinary skill in the art would have been motivated and had a reasonable expectation success in arriving at the claimed invention based on the two cited references is simply inaccurate and clearly misconstrues the level of skill required in the art. Appellants submit that the Examiner has failed to establish a *prima facie* case of obvious by failing to set forth the requisite teaching, suggest or motivation for the asserted combination.

Appellants note that, even if the Examiner were to assert the same rejection based on a

obviousness rational other than the TSM test, e.g. rationales 1-6 set forth above, such rationales expressly require that the results be predictable or that there be a reasonable expectation of success. As set forth above, formulation of transdermal drug delivery systems is a highly complex art and is particularly unpredictable and complicated when formulating with a permeation enhancer. Accordingly, Appellants assert that the cited combination of references would similarly fail to establish a *prima facie* case of obvious under any of such obvious rationales.

Further, Appellants note that, although U.S. '178 sets forth a lengthy laundry list of possible permeation enhancers and/or cell envelope disordering compounds which can be used in the matrix patches, including the broad category of "saturated and unsaturated fatty acids and their esters," the only teaching of a fatty acid ester of lactic acid as a permeation enhancer is found in Example 11. Example 11 is drawn to specific transdermal formulations for diclofeanc, buspirone, and clonidine, each of which is not only distinct drug from Huperzine, but is also in a distinct family of drugs far removed from Huperzine. Nothing in U.S. '178 correlates or connects the use of lactic acid esters, or any other permeation enhancer, with Huperzine or any other Anti-Parkinson drug. As set forth above, the identification and correlation of specific permeation enhancers with specific drugs is "difficult to predict" and "must be carefully analyzed and demonstrated by empirical work." Accordingly, Appellants submit that the indiscriminate combination of the transdermal system of U.S. 715 with a permeation enhancer found in U.S. '178 without teaching, suggestion or motivation for such a combination found in the references themselves or in the knowledge of one of ordinary skill in the art, and without having a reasonable likelihood of success is evidence of impermissible hindsight reconstruction.

As noted by the Examiner in her final office action, reconstruction based upon hindsight

reasoning is permissible only "so long as it takes into account only knowledge which was within the level of the ordinary skill at the time the claimed invention was made and does not include knowledge gleaned only from the applicant's disclosure…" *In re Mclaughlin,* 443 F.2d 1392 (emphasis added). As described above, at the time of the present invention, and continuing through the present day, the knowledge of one of ordinary skill in the art was and is not sufficient to cause one of ordinary skill to have combined the teachings of the asserted references. Appellants respectfully submit that the Examiner has only arrived at the claimed invention from the cited references by using knowledge which was gleaned from the Appellants' disclosure. Accordingly, Appellants submit that the asserted combination of references is improper because it relies on impermissible hindsight.

Lastly, the Examiner has conceded that the presently claimed blood plasma levels of Huperzine are not taught by U.S. '715 or by U.S. '178, but continues to assert that such blood plasma levels could be readily determined by one having ordinary skill in the art and are inherently taught by U.S. '715. Appellants continue to dispute these assertions and respectfully submit that the cited references fail to teach the blood plasma level claim limitation. Specifically, Appellants dispute that the claimed blood plasma levels could be readily achieved through simple experimentation or "tinkering" with other transdermal formulations. Blood plasma levels are the key of the formulation design of transdermal delivery system, which is affected by numerous factors including selection of proper adhesive, selection of proper permeation enhancers and their quantity, drug load, delivery rate, and depletion rate. Further, the present claims require specific blood plasma levels for a period of at least three days. The Examiner's assertion that the teaching by U.S. '715 of overlapping delivery rates is sufficient to constitute inherent disclosure of the claimed blood plasma level is simply incorrect. As set forth

above, drug delivery rate alone is not determinative of blood plasma levels, but rather only one of a myriad of interconnected factors. In light of this, Appellants submit that the cited combination of U.S. '715 and U.S. '178 do not teach each and every claim element of the pending claims, namely the required blood plasma levels for the claimed period of time.

D. Conclusion

In conclusion, Appellants respectfully submit that the claims on appeal set forth in the Appendix are patentable over the cited references. Particularly, the Examiner has failed to establish a *prima facie* case of obviousness by: 1) Failing to demonstrate the requisite teaching, suggestion, or motivation in the references themselves or in the knowledge of one ordinary skill in the art to form the asserted combination of references; 2) Improperly utilizing hindsight reconstruction to generate the assert combination of references; and 3) Failure of the references to teach each and every element of the pending claims, namely the blood plasma levels and duration.

In light of the above, Appellants respectfully submit that all remaining rejections are improper, and should be overturned.

Dated this 12th day of February, 2009.

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VIII. CLAIMS APPENDIX

Claims 1-52: (canceled)

53. (withdrawn) A transdermal formulation for improving memory and cognitive function comprising:

an inert carrier having from about 0.01 % w/w to about 20% w/w of huperzine admixed therewith, and including a permeation enhancer selected from the group consisting of: fatty acids, fatty acid esters, fatty alcohols, amides, pyrrolidones, glycerol triesters, terpenes, their salts, and mixtures thereof, wherein said formulation provides a huperzine blood plasma level of from about 0.1 ng/ml to about 30 ng/ml, upon administration to a subject.

54. (withdrawn) The transdermal formulation of claim 53, wherein the blood plasma level attained is from about 0.5 to about 15 ng/ml.

55. (withdrawn) The transdermal formulation of claim 53, wherein the blood plasma level is achieved within about 0.5 to about 48 hours after administration of the formulation.

56. (withdrawn) The transdermal formulation of claim 53, wherein a single dose is sufficient to sustain the huperzine blood plasma level for a duration of at least about 3 days.

57. (withdrawn) The transdermal formulation of claim 53, wherein a single dosage is

sufficient to sustain the huperzine blood plasma level for a duration at least about 7 days.

58. (withdrawn) The transdermal formulation of claim 53, wherein the huperzine is a member selected from the group consisting of huperzine A, huperzine B, huperzine X, and salts, analogs, derivatives, prodrugs, and mixtures thereof.

59. (withdrawn) The transdermal formulation of claim 58, wherein the huperzine is huperzine A.

60. (withdrawn) The transdermal formulation of claim 58, wherein the huperzine is huperzine B.

61. (withdrawn) The transdermal formulation of claim 58, wherein the huperzine is huperzine X.

62. (withdrawn) The transdermal formulation of claim 53, wherein the inert carrier comprises a pressure sensitive adhesive, and the formulation is an adhesive matrix patch.

63. (withdrawn) The transdermal formulation of claim 53, wherein the inert carrier is a liquid reservoir, and the formulation is a liquid reservoir system.

64. (withdrawn) The transdermal formulation of claim 53, wherein the formulation is a topical formulation.

65. (withdrawn) The transdermal formulation of claim 53, wherein the permeation enhancer is selected from the group consisting of: a terpene compound, lauromide DEA, glycerol monooleate, sorbitan monooleate, lauryl alcohol, triacetin, cineole, oleic acid, and mixtures thereof.

66. (withdrawn) The transdermal formulation of claim 53, wherein said huperzine further comprises a huperzine hybrid compound.

67. (withdrawn) The transdermal formulation of claim 66, wherein said huperzine hybrid compound is a huperzine-tacrine hybrid.

68. (withdrawn) The transdermal formulation of claim 53, further comprising a hormone admixed with the carrier.

69. (withdrawn) The transdermal formulation of claim 53, wherein the hormone is a member selected from the group consisting of estrogens, androgens, melatonin, seratonin, DHEA, phosphatidyl serine, and mixtures thereof.

70. (withdrawn) The transdermal formulation of claim 69, wherein the hormone is estrogen.

71. (withdrawn) The transdermal formulation of claim 53, further comprising a treatment

agent selected from the group consisting of antipsychotics, anxiolytics, antidepressants, and mixtures thereof.

72. (withdrawn) The transdermal formulation of claim 71, wherein the treatment agent is an antipsychotic.

73. (withdrawn) The transdermal formulation of claim 71, wherein the treatment agent is an anxiolytic.

74. (withdrawn) The transdermal formulation of claim 71, wherein the treatment agent is an antidepressant.

75. (withdrawn) The transdermal formulation of claim 53, further including a positive health benefit imparting substance selected from the group consisting of: vitamins, amino acids, anti-oxidants, and mixtures thereof.

76. (withdrawn) The transdermal formulation of claim 75, wherein the positive health benefit imparting substance is a vitamin.

78. (withdrawn) The transdermal formulation of claim 75, wherein the positive health benefit imparting substance is an amino acid.

79. (withdrawn) The transdermal formulation of claim 75, wherein the positive health

benefit imparting substance is an anti-oxidant.

80. (withdrawn) A transdermal formulation for improving memory and cognitive function consisting essentially of:

a mixture of an inert carrier and huperzine in an amount of from about 0. 01% w/w to about 20% w/w, which provides a huperzine blood plasma level of from about 0.1 to about 30 ng/ml upon administration to a subject.

81. (previously presented) A method of improving memory and cognitive function in a subject, comprising:

transdermally administering huperzine to the subject from a transdermal matrix patch that includes an adhesive matrix with an acrylate polymer including homopolymers, copolymers, or terpolymers, or rubber-based pressure sensitive adhesive including copolymers and a fatty acid ester of lactic acid as a permeation enhancer, said matrix patch excluding Azone, in order to provide a huperzine blood plasma level of from about 0.1 to about 30 ng/ml for a duration of at least about 3 days from a single transdermal administration.

82. (previously presented) The method of claim 81, wherein the huperzine is a member selected from the group consisting of huperzine A, huperzine B, huperzine X, and salts, analogs, prodrugs, and mixtures thereof.

83. (previously presented) The method of claim 81, wherein the blood plasma level is from about 0.5 to about 15 ng/ml.

84. (previously presented) The method of claim 81, wherein the huperzine blood plasma level is attained within about 0.5 to about 48 hours after initiation of the huperzine administration.

85. (canceled)

86. (previously presented) The method of claim 81, wherein the huperzine blood plasma level is sustained for a duration of at least 7 days from a single transdermal administration.

87. (withdrawn) A method of improving memory and cognitive function in a subject, comprising:

transdermally administering a huperzine formulation with a hormone to the subject which provides a huperzine blood plasma level of from about 0.1 to about 30 ng/ml.

88. (withdrawn) The method of claim 81, wherein the hormone is a member selected from the group consisting of estrogens, androgens, melatonin, seratonin, DHEA, phosphatidyl serine, and mixtures thereof.

89. (withdrawn) The method of claim 88, wherein the hormone is estrogen.

90. (withdrawn) A method of improving memory and cognitive function in a subject, comprising:

transdermally administering a huperzine formulation with a treatment agent selected from the group consisting of antipsychotics, anxiolytics, antidepressants, and mixtures thereof, to the subject which provides a huperzine blood plasma level of from about 0.1 to about 30 ng/ml.

91. (withdrawn) The method of claim 90, wherein the treatment agent is an antipsychotic.

92. (withdrawn) The method of claim 90, wherein the treatment agent is an anxiolytic.

93. (withdrawn) The method of claim 90, wherein the treatment agent is an antidepressant.

94. (withdrawn) The method of claim 90, further comprising co-administering to the subject a positive health benefit imparting substance selected from the group consisting of: vitamins, amino acids, anti-oxidants, and mixtures thereof.

95. (withdrawn) The method of claim 94, wherein the positive health benefit imparting substance is a vitamin.

96. (withdrawn) The method of claim 94, wherein the positive health benefit imparting substance is an amino acid.

97. (withdrawn) The method of claim 94, wherein the positive health benefit imparting

substance is an anti-oxidant.

98-101. (canceled).

102. (previously presented) The method of claim 81, wherein the transdermal patch comprises an acrylic adhesive matrix patch.

103. (previously presented) The method of claim 81, wherein the huperzine blood plasma level is attained within about 0.5 to about 10 hours after initiation of the huperzine administration.

IX. EVIDENCE APPENDIX

(None)

X. RELATED PROCEEDINGS APPENDIX

(None)